IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BLAKE et al — Atty. Ref.: 39-187; Confirmation No. 4136

Appl. No. 09/367,261 — TC/A.U. 1625

Filed: February 28, 2000 — Examiner: Dentz, B.

For: DRUG TARGETING

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April 19, 2006

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE

This is in response to the Office Action dated December 21, 2005, in the above, the period for response having been extended up to April 21, 2006, by submission of the required petition and fee herewith.

The following is responsive to the Examiner's requirement for election.

The present application relates to bioreductive drug conjugates for use in targeting of therapeutic agents to localized regions of hypoxic and/or ischemic tissue within the body. The conjugates comprise a bioreductive moiety linked to a therapeutic agent. At a hypoxic/ischemic site, the bioreductive moiety undergoes bioreduction to generate release of the therapeutic agent which has therefore been targeted to the hypoxic ischemic site.

It is an important feature of the invention that the residue of the bioreductive moiety (i.e. after bioreduction thereof) is non-cytotoxic and in particular does not undergo reaction with biomolecules. The application as filed describes two "mechanisms" by which it may be ensured that the reduced form of the bioreductive moiety does not undergo reaction with a biomolecule.

One such mechanism is disclosed in general terms at page 6, lines 9-18 of the specification and is based on the feature that on bioreduction of the bioreductive moiety (to effect release of the therapeutic agent) the original bioreductive moiety gives rise to a self-alkylating species so that there is an intramolecular alkylation reaction within said species which occurs in preference to alkylation of any biomolecule such as DNA. Claim 1 is directed to this feature.

A further "mechanism" disclosed in the application for generating a non-cytoxic residue of the bioreductive moiety is as disclosed in the paragraph bridging pages 6 and 7 of the specification. In this embodiment, the bioreductive moiety is such that, on bioreduction (to release the therapeutic agent), there is generated an alkylating center which is sterically hindered thus abolishing alkylating reactivity and preventing alkylation of biomolecules. This is the subject of independent claim 18.

The Examiner requires election of a single species to which the claims will be restricted if no generic claim is finally held to be allowable. The basis for the election requirement appears to be that the Examiner considers the current broad claims to be anticipated by Mehta et al.

In order to comply with the Official Action, Applicants elect compound (8) from Example 3 of the specification (see page 30). This is a "model" compound in which the

"R" group is intended to represent a drug species that is eliminated on bioreduction of the bioreductive moiety. This is represented by the final two steps of the reaction sequence shown on page 30 of the specification. The important "part" of the structure of compound (8) is the indoloquinone residue since in effect the drug is "incidental" in the sense that it is the indoloquinone moiety that is capable of undergoing bioreduction at a hypoxic/ischemic site to effect elimination of the drug.

Compound (8) is covered by claim 1 and by claims 2-5. Additionally, it is an example of a compound of formula (IV) as defined in claim 11. It is also covered by the preferred definition for formula (IV) given in claim 12. More specifically, with regard to claims 11 and 12, compound (8) is an example of formula (IV) in which:

S and T together with the intervening ring carbon atoms form a quinone ring,

q = 0 (so there are no R^3 and R^4 groups),

R^5 is a hydrogen atom,

R^7 is methyl,

Z represents a group of the formula $-CH_2CH_2OH$, and

E represents the residue of a therapeutic agent (which could be considered to be attached via an oxygen atom as a linking group L).

Compound (8) is also covered by claim 13 for the case where the bioreductive moiety is an indoloquinone.

The process for producing compound (8) could be viewed to be covered by claim 19.

As mentioned above, the election requirement has been raised because the Examiner is of the view that the claimed bioreductive conjugates are anticipated by Mehta et al. Applicants do not agree with the Examiner's view.

Mehta et al disclose probes for use in detecting hypoxic tissue and as post-irradiation radio sensitizers. Mehta relates to a nitroimidazole (as a bioreductive moiety) linked via a C_4-alkylelene chain to the 8-position of a theophylline nucleus. The paper also discloses the previously used isomers in which the alkylene chain is linked to the 7-position of the theophylline ring.

The compounds disclosed are able to function as a probe for hypoxic tissue. More particularly, if such hypoxic tissue is present then the nitroimidazole nucleus is targeted thereto and the presence of the tissue is confirmed by the use of immunochemical reagents to detect the theophylline.

The compounds can also be used as a post-irradiation sensitizer of irradiated hypoxic cells in killing by X-rays.

The technique disclosed in the cited paper relies on the bioreducible moiety and side-chain remaining conjugated after reduction, in complete contrast to the subject matter of the present application where reductively activated elimination of a substituent is central to the invention. Consequently, the paper does not disclose or suggest the concept of the bioreductive moiety being converted to a self-alkylating species (claim 1) or a species incorporating a sterically hindered alkylating center (claim 18).

An earlier and favorable Action on the merits is requested.

Respectfully submitted,

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